REMARKS/ARGUMENTS

Claims 47 and 69-74 are pending and under consideration, claims 1-46 and 48-68 having been canceled and new claims 72-74 having been added. Support for human IgG1 isotype in amended claim 47 is provided at, e.g., p. 18, lines 15-18. Claims 69 and 70 (which are free of the cited art) have been rewritten in independent form. Support for the amendment to recite a chimeric, humanized or human antibody in new claim 72 is provided at *e.g.*, pp. 21-28. Support of a sustained release composition in new claims 73 and 74 is provided at, e.g., p. 37, lines 32-33. No amendment should be construed as an acquiescence in any ground of rejection.

The specification has been amended to (1) recite the priority claim under 35 U.S.C. § 120; (2) conform with the replacement drawing sheets submitted herewith; (4) correct obvious errors; and, (3) identify two cell lines producing the 10D5 and 3D6 antibodies, respectively, deposited with the ATTC. Thus, the amendments to the specification contain no new matter.

The specification has been amended to conform with the replacement drawing sheets submitted herewith. The paragraphs beginning on page 7, line 14 and p. 59, line 25 describe Figure 10, and to conform with the amended Figure 10 both paragraphs have been amended to identify the upper and lower panels of Figure 10 as Figures 10A and 10B, respectively. The paragraph beginning on page 7, line 27 of the specification describes Figure 15. The paragraph has been replaced with six replacement paragraphs, which describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraphs beginning on p. 7, line 32 and p. 8, line 5 describe Figures 19 and 20, respectively; and, to conform with the amendment to Figures 19 and 20 have been amended to delete "The results for peptide sequence VGSNKGAIIG (SEQ ID NO:32) are shown twice." The paragraphs beginning on page 76, line 17, and page 77, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998, which is incorporated herein by reference. The paragraph beginning on page 80, line 1 has been amended to identify Figures 15A-15E.

The specification has been amended to correct obvious errors. The paragraphs beginning on p. 16, line 16 and p. 62, line 12 have been amended to replace the plain text font of genus and species names with an italicized font, *e.g.*, "Salmonella" has been replaced with "*Salmonella.*" The paragraph beginning on page 46, line 19 has been amended to correct an obvious error, *i.e.*, "that binds to A to the patient" has been amended to recite, "that binds to Aβ in the patient" and "of Aβdo not" has been amended to recite "of Aβ do not show."

Applicants deposited the cell line producing the antibody 10D5 and the cell line producing the antibody 3D6 with the ATCC on April 8, 2003. Applicants submit a statement under MPEP § 2406.02 herewith. The cell lines deposited with the ATCC are the cell lines producing the antibodies 10D5 and 3D6, respectively, which are identified in the instant specification and in Application No. 09/580,518, filed May 26, 2000. Applicants have amended the paragraphs beginning on p. 68, line 17, p. 83, line 14, and p. 107, line 26 of the specification to recite the depository, accession number, and deposit date of the cell lines producing the 10D5 and 3D6 antibodies, respectively. These amendments do not add new matter (*see* In re Lundak, 227 USPQ 90 (Fed. Cir. 1985) and MPEP § 2406.01).

Election/Restriction

¶1. Withdrawal of the species requirement is acknowledged.

Sequence Requirements

¶3. The Office Action takes the position that the instant application fails to comply with 37 C.F.R. §§ 1.821-1.825 because Figures 19 and 20 disclose an amino acid sequence without an appropriate SEQ ID NO. As discussed in the Amendments to the Drawings section, Figures 19 and 20 have been amended to delete one of the two occurrences of the sequence "VGSNKGAIIG." As discussed above, the specification has been amended to conform to the replacement drawing sheet showing Figure 19 and the replacement drawing sheet showing Figure 20.

Drawings

¶4. Figure 10 was objected to because the upper and lower panels were unlabeled. The replacement Figure 10 drawing sheet, attached hereto, has been amended to identify the top panel as "10A" and the bottom panel as "10B." The specification has been amended to conform to the replacement Figure 10 drawing sheet.

¶5. Figure 11 was objected to because it lacked an appropriate legend. Figure 11 has been amended to include a legend which indicates the treatment group. Support for the amendment to Figure 11 is found at, *e.g.*, p. 7, lines 14-15; and, p. 62, line 23 to p. 63, line 11.

Non-Statutory Double Patenting

U.S. Application No. 10/010,942

¶6. Claims 47 and 61-71 stand provisionally rejected for obviousness type double patenting over claims 1-57, 62, 84-131, and 137 of U.S. Application No. 10/010,942. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited case provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

U.S. Application Nos. 09/724,552 and 09/724,551

¶7. Claims 47 and 67-71 stand provisionally rejected for obviousness type double patenting over claims 47 and 67-71 of U.S. Application No. 09/724,552 and claim 47 of U.S. Application No. 09/497,551. In light of the fact that U.S. Application No. 09/724,551 is the instant application, the rejection over claim 47 is moot. Applicants propose the rejection over claims 47 and 67-71 of U.S. Application No. 09/497,552 be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited case provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election

of species, and the claims of U.S. Application No. 09/497,552 are in conflict with those in the present case at this time.

U.S. Application Nos. 09/979,701 and 09/724,273

¶8. Claims 47 and 67-71 stand provisionally rejected for obviousness type double patenting over claims 88 and 108-109 of U.S. Application No. 09/979,701 and claims 47 and 67-68 of U. S. Application No. 09/724,273. The rejection of claims 47, 67, and 69-71 over claims 47 and 67-68 of U.S. Application No. 09/724,273 is moot in light of the cancellation of claims 47 and 67-68. Applicants request the rejection over claims 88 and 108-109 of U.S. Application No. 09/979,701 be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited case provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims of U.S. Application No. 09/979,701 are in conflict with those in the present case at this time.

Claim Rejections

Rejection of Claim 47 Under 35 U.S.C. § 112, Second Paragraph

¶9. Claim 47 stands rejection for omitting the word epitope from the claim. The claim has been amended as suggested.

Rejection of Claims 47, 67, 68, and 71 Under 35 U.S.C. § 102(b) as Allegedly Anticipated by Walker

¶¶10-11. Claims 47 and 71 stand rejected as anticipated by Walker. Walker is alleged to disclose the 10D5 antibody and an epitope specificity of Aβ1-16. The Examiner notes the present specification indicates 10D5 has an epitope specificity of Aβ3-6. The Examiner alleges that Walker teaches using 10D5 in a saline solution which the Examiner alleges is a pharmaceutical composition.

Claim 47 (and claims dependent therefrom) specify that the claimed antibodies have a *human* IgG1 isotype. Such is present, for example, in human antibodies, humanized antibodies or chimeric antibodies of the IgG1 isotype. Although practice of the claimed

invention is not dependent on an understanding of mechanism, it is believed that the use of antibodies with a human IgG1 isotype is advantageous because this isotype has the highest affinity of human isotypes for the human FcRI receptor on phagocytic cells, and phagocytic cells effect the clearing response of amyloid deposits of Aβ (*see* specification at p. 18, lines 15-17 and Table 16 at p. 97).

The 10D5 antibody discussed by Walker is a mouse antibody having *mouse* IgG1 isotype (see Table 16 at p. 97). Not only is mouse IgG1, not a human isotype, it is not even the closest mouse equivalent of human IgG1. As discussed in the specification, the closest mouse equivalent of human IgG1 is mouse IgG2a (*see* p. 21, lines 18-19). Thus, Walker does not disclose or suggest an antibody having a human IgG1 isotype as claimed.

Applicants respectfully submit that Walker does not anticipate new claims 72 and 74 because Walker does not disclose a chimeric, humanized or human antibody.

Nor would Walker render new claims 72 and 74 obvious for at least the following reasons. First, unlike anticipation, obviousness cannot be based on inherency. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Rijkckaert*, 28 U.S.P.Q.2d at 1957 (Fed. Cir. 1993). Here, as the Examiner has acknowledged, Walker does not disclose the binding specificity of the 10D5 antibody. Walker also does not provide any indication that the 10D5 antibody would be better than any other antibody to Aβ for *in vivo* labelling of Aβ deposits, much less as a pharmaceutical composition. Without knowing the binding specificity of the 10D5 antibody, or any indication that this binding specificity would be an advantage, there would be no motivation to use antibodies that bind to an epitope within Aβ1-7 as claimed.

Second, Walker would not have provided motivation to make a chimeric, humanized or human antibody. As noted above, such antibodies are made for the purpose of avoiding or reducing immunogenic responses when the antibodies are administered to humans. Walker does not provide any reasonable expectation that antibodies could be used for *in vivo* diagnosis of Alzheimer's disease in humans without further invention. Walker actually conducted his experiments on a rhesus monkey and injected his antibody directly into the CNS. Walker notes that the extent of labelling was incomplete ("intracistinernally injected antibody

failed to reach a significant number of deposits") (at p. 382, second paragraph). Walker also notes that intracistinal injection or other techniques used to circumvent the blood brain barrier are "not suitable for routine therapeutic or diagnostic purposes" (at p. 382, second paragraph). Walker also considers the alternative route of delivering antibodies by the blood but implies that techniques for facilitating transport of large molecule across the blood-brain barrier first need to be developed or refined (*id*). Walker also states that the "blood-brain barrier prevents the passage of many types of molecules from the bloodstream to the brain . . . rendering vascular delivery of ligands to Aβ problematic" (at p. 377, first column, first paragraph). Walker concludes only that it "*may eventually* be feasible to employ antibodies to deliver therapuetic agents directly to Aβ in the brain, or in combination with imaging technologies, such as PET or SPECT, to diagnose β-amyloidoses in living subjects" (at p. 381, first column, second paragraph, emphasis supplied). Because of the limited results obtained by Walker, the potential difficulties envisaged by Walker in delivering antibody to humans, and the tentative nature of Walker's conclusion, one would not have reasonably expected Walker's approach could be used for diagnosis in humans without further invention. Without such expectation one would not have been motivated to produce a chimeric, humanized or human antibody for use in the claimed methods.

Third, assuming arguendo that one were considering producing a chimeric or humanized version of antibody 10D5, then one would require knowledge of, or ability to determine, the DNA sequence of nucleic acids encoding the heavy and light chains of the 10D5 antibody. Walker does not disclose these nucleic acid sequences. Further, although it might be a routine matter to determine such sequences when one has a hybridoma expressing the antibody, Walker does not provide an enabling disclosure of such a hybridoma. Applicants have amended the specification to include reference to the cell line producing the antibody 10D5 and the cell line producing the antibody 3D6, both of which were deposited with the ATCC on April 8, 2003.

Rejection of Claims 47, 67, 68, and 71 Under 35 U.S.C. § 102(b) as Allegedly Anticipated by Schenk

¶¶12-13. Claims 47 and 71 stand rejected as anticipated by Schenk, US 5,593,846. Schenk is alleged to disclose the 10D5 antibody. Schenk is also alleged to teach

using 10D5 in a buffer solution, which the Examiner alleges is a pharmaceutical composition (citing to col. 14, line 45-60). Schenk is distinguished for at least the same reasons as Walker. As in Walker, the 10D5 antibody is a mouse antibody and has mouse IgG1 isotype. Further, Schenk uses 10D5 only as a research reagent to detect Aβ in various assays. Schenk does not disclose or suggest producing humanized, chimeric or human antibodies binding to an epitope within Aβ1-7, as claimed.

It is also noted that the section of Schenk cited by the Examiner for disclosure of a pharmaceutical composition containing 10D5 (col. 14, lines 34-60) actually describes the buffer of the immunogen used to generate 10D5, not the buffer of 10D5 itself. Thus, this passage does not disclose a pharmaceutical composition comprising 10D5.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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